Dr. Robert Yarchoan Excerpt 3

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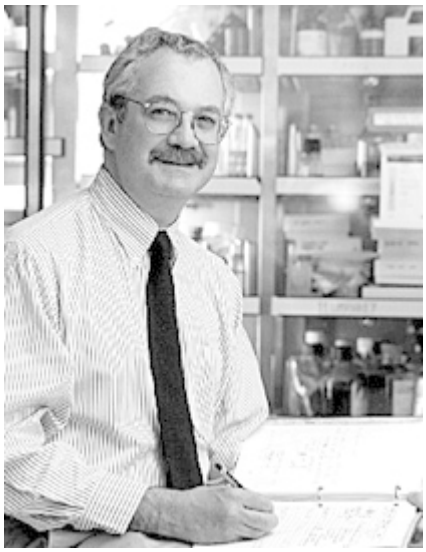
Audio Transcript



Dr. Robert Yarchoan

Interviewer: When you got to the Phase 1 trials in July 1985, I believe, what happened? Would you walk us through the process?

Yarchoan: The trial included 19 patients. We treated 11 and Duke treated 8. My best recollection is that the draft protocol was originally written by people from Burroughs with a fair amount of consultation from Sam [Broder]. We had sent down a copy of our suramin protocol, and then Sam had communicated to them things that we would have done differently based on what we had learned from that protocol. So it incorporated their expertise in terms of doing Phase 1 testing and such, and what we had been learning from the suramin study. We then made some changes to the study. The Burroughs researchers were also interested in having something done down there, I think, because they knew people at Duke and they could go across town and see the patients. So it was agreed that the protocol would be done at Duke and at the NCI, and we would take the lead on it.

We got the protocol through the IRB. Then my recollection is that the first patient–I may be off a day–came in on July 3 and was treated July 5, or something like that, up on 13 East. And the first treatment was an intravenous infusion. The first patient to receive AZT was from Boston. He had full-blown AIDS, he had had *Pneumocystis carinii* pneumonia, and he had about, 40 or so CD4 cells per cubic millimeter.

Interviewer: That is not many!

Yarchoan: The patient received an infusion that was for the initial testing for pharmacokinetics, and Sam and I sat around and watched as he got a syringe full of AZT. I remember that night he developed a fever, and we came in and tried to figure out what the cause was–was this drug toxicity or was it the disease. We could not figure out what was going on. The temperature was not high enough to stop the treatment, and it looked like it was consistent with some sort of minor opportunistic infection or a cold, and so we continued on. The fever then went away.

He perked along, receiving the drug three times a day intravenously. It was initially supposed to be a two-week protocol. At the end of the two weeks, we found that his CD4 count had gone up, and we did not know what to make of this. We knew that CD4 counts bounced around, but this was a bounce in the right direction. We thought we had enough to push the company and the FDA to extend the treatment, so we got an amendment to extend it for another two weeks. The CD4 count was up around 200 by then. It was also getting really tiresome to give this drug three times a day intravenously, and there was reasonable evidence from the animal studies that it could be given by mouth. So we got permission to amend the protocol to change to give it by mouth. The patient received another four weeks of treatment by mouth. His CD4 count did not get much higher. It bounced around and actually was dropping back down by the end of the eight weeks. I guess, in retrospect, we were also learning about resistance in that first patient, just the way the first patient with AIDS that we saw was like the whole epidemic rolled into one patient.

But he really felt a lot better. We also were doing skin tests, and we found out after a few weeks that his skin test–which is a way of measuring the T-cell responsiveness–had changed. He was anergic at the beginning of therapy, which means he did not respond to any of the four test antigens. At the end of a few weeks of AZT, he had a very robust skin test to tuberculosis. This was a PPD [purified protein derivative] test. So, again, in the sense that these initial patients were really textbooks–there was the tie-in with tuberculosis and HIV that we now appreciate in this patient. But we were very impressed that not only were the number of CD4 cells going up, but they were working.

Then we started getting concerned that this was an artifact that occurred just because we were immunizing him by giving him repeated shots. Normally you do not apply PPDs every few weeks. We found some articles related to this. The literature was pretty murky, but the sense we got is that if someone were truly anergic, they would not have a positive skin test to an antigen if you retested them a few weeks later. That made us feel fairly confident that this was something real. So we were excited about this patient, and we wrote to the FDA and Burroughs Wellcome.

Meanwhile, the second patient that we had treated at this dose had severe Kaposi's sarcoma, and this Kaposi's progressed while he was on AZT and he had a minor CD4 count increase. There was another patient that was treated down at Duke. He started at about 200 CD4 cells, and his count went up a little bit. And there was a fourth patient that we treated that started with five CD4 cells and went up to 10, then dropped back down to five again. So, in retrospect, they all moved in the right direction. But it was just this first patient that really looked like something.

Then we went to the second dose, in which I think we doubled the dose. And six out of six patients at that dose had an increase in their CD4 cells. At a certain point, we did the statistics. And around October, we realized that we were having statistically significant increases in the CD4 cells. It was just over the level of being statistically significant. We were, at that point, very, very excited that we really had something. The one reliable test that we had at that point was the CD4 count. We did not have any truly accurate viral load studies. We had a culture technique, but it was hard to know what it was telling us, and the results were coming in all over the board. But it was the immunologic changes that impressed us–they were relatively small, but they were always in the right direction.

Interviewer: You are presenting a picture of seeing through a glass darkly and just trying hard to find a way.

Yarchoan: Yes. We have used the analogy of seeing a ship in the fog. You see these patterns and you are never sure whether there is really a ship coming or just eddies in the fog.

For the complete transcript of this interview, go to the Transcripts page.